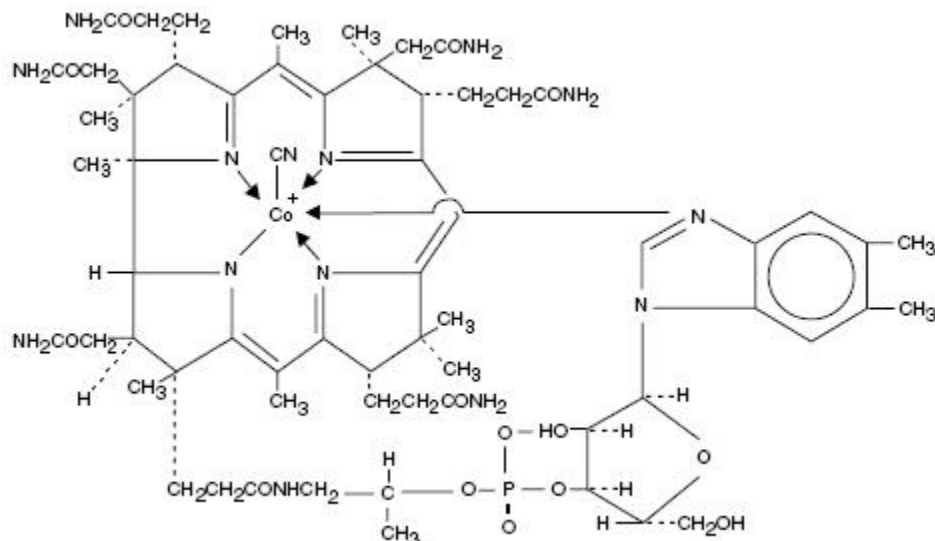


NASCOBAL - cyanocobalamin spray

Par Pharmaceutical, Inc

DESCRIPTION

Cyanocobalamin is a synthetic form of vitamin B₁₂ with equivalent vitamin B₁₂ activity. The chemical name is 5,6-dimethylbenzimidazolyl cyanocobamide. The cobalt content is 4.35%. The molecular formula is C₆₃H₈₈CoN₁₄O₁₄P, which corresponds to a molecular weight of 1355.38 and the following structural formula:



Cyanocobalamin occurs as dark red crystals or orthorhombic needles or crystalline red powder. It is very hygroscopic in the anhydrous form, and sparingly to moderately soluble in water (1:80). Its pharmacologic activity is destroyed by heavy metals (iron) and strong oxidizing or reducing agents (vitamin C), but not by autoclaving for short periods of time (15-20 minutes) at 121°C. The vitamin B₁₂ coenzymes are very unstable in light.

Nascobal[®] Nasal Spray is a solution of Cyanocobalamin, USP (vitamin B₁₂) for administration as a spray to the nasal mucosa. Each bottle of Nascobal Nasal Spray contains 2.3 mL of a 500 mcg / 0.1 mL solution of cyanocobalamin with sodium citrate, citric acid, glycerin and benzalkonium chloride in purified water. The spray solution has a pH between 4.5 and 5.5. The spray pump unit must be fully primed (see **DOSAGE AND ADMINISTRATION**) prior to initial use. After initial priming, each spray delivers an average of 500 mcg of cyanocobalamin and the 2.3 mL of spray solution contained in the bottle will deliver 8 doses of Nascobal Nasal Spray. The unit must be re-primed before each dose. (See **DOSAGE AND ADMINISTRATION**.)

CLINICAL PHARMACOLOGY

GENERAL PHARMACOLOGY AND MECHANISM OF ACTION

Vitamin B₁₂ is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (e.g., epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for vitamin B₁₂. Vitamin B₁₂ can be converted to coenzyme B₁₂ in tissues, and as such is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine, a reaction which also requires folate. In the absence of coenzyme B₁₂, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyltetrahydrofolate, and a functional folate deficiency occurs. Vitamin B₁₂ also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B₁₂ is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B₁₂ deficiency results in megaloblastic anemia, GI lesions, and neurologic damage that begins with an inability to produce myelin and is followed by gradual degeneration of the axon and nerve head.

Cyanocobalamin is the most stable and widely used form of vitamin B₁₂, and has hematopoietic activity apparently identical to that of the antianemia factor in purified liver extract. The information below, describing the clinical pharmacology of cyanocobalamin, has been derived from studies with injectable vitamin B₁₂.

Vitamin B₁₂ is quantitatively and rapidly absorbed from intramuscular and subcutaneous sites of injection. It is bound to plasma proteins and stored in the liver. Vitamin B₁₂ is excreted in the bile and undergoes some enterohepatic recycling. Absorbed vitamin B₁₂ is transported via specific B₁₂ binding proteins, transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B₁₂ storage.

Parenteral (intramuscular) administration of vitamin B₁₂ completely reverses the megaloblastic anemia and GI symptoms of vitamin B₁₂ deficiency; the degree of improvement in neurologic symptoms depends on the duration and severity of the lesions, although progression of the lesions is immediately arrested.

Gastrointestinal absorption of vitamin B₁₂ depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with subacute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B₁₂ prevents progression of neurologic damage.

The average diet supplies about 4 to 15 mcg/day of vitamin B₁₂ in a protein-bound form that is available for absorption after normal digestion. Vitamin B₁₂ is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin B₁₂ is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B₁₂ enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B₁₂.

Colchicine, para-aminosalicylic acid, and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B₁₂.

PHARMACOKINETICS

Absorption

A three way crossover study in 25 fasting healthy subjects was conducted to compare the bioavailability of the B₁₂ nasal spray to the B₁₂ nasal gel and to evaluate the relative bioavailability of the nasal formulations as compared to the intramuscular injection. The peak concentrations after administration of intranasal spray were reached in 1.25 +/- 1.9 hours. The average peak concentration of B₁₂ obtained after baseline correction following administration of intranasal spray was 757.96 +/- 532.17 pg/mL. The bioavailability of the nasal spray relative to the intramuscular injection was found to be 6.1%. The bioavailability of the B₁₂ nasal spray was found to be 10% less than the B₁₂ nasal gel. The 90% confidence intervals for the log_e-transformed AUC_(0-t) and C_{max} was 71.71% - 114.19% and 71.6% - 118.66% respectively.

In pernicious anemia patients, once weekly intranasal dosing with 500 mcg B₁₂ gel resulted in a consistent increase in pre-dose serum B₁₂ levels during one month of treatment (p < 0.003) above that seen one month after 100 mcg intramuscular dose (Figure).

Distribution

In the blood, B₁₂ is bound to transcobalamin II, a specific B-globulin carrier protein, and is distributed and stored primarily in the liver and bone marrow.

Elimination

About 3-8 mcg of B₁₂ is secreted into the GI tract daily via the bile; in normal subjects with sufficient intrinsic factor, all but about 1 mcg is reabsorbed. When B₁₂ is administered in doses which saturate the binding capacity of plasma proteins and the liver, the unbound B₁₂ is rapidly eliminated in the urine. Retention of B₁₂ in the body is dose-dependent. About 80-90% of an intramuscular dose up to 50 mcg is retained in the body; this percentage drops to 55% for a 100 mcg dose, and decreases to 15% when a 1000 mcg dose is given.

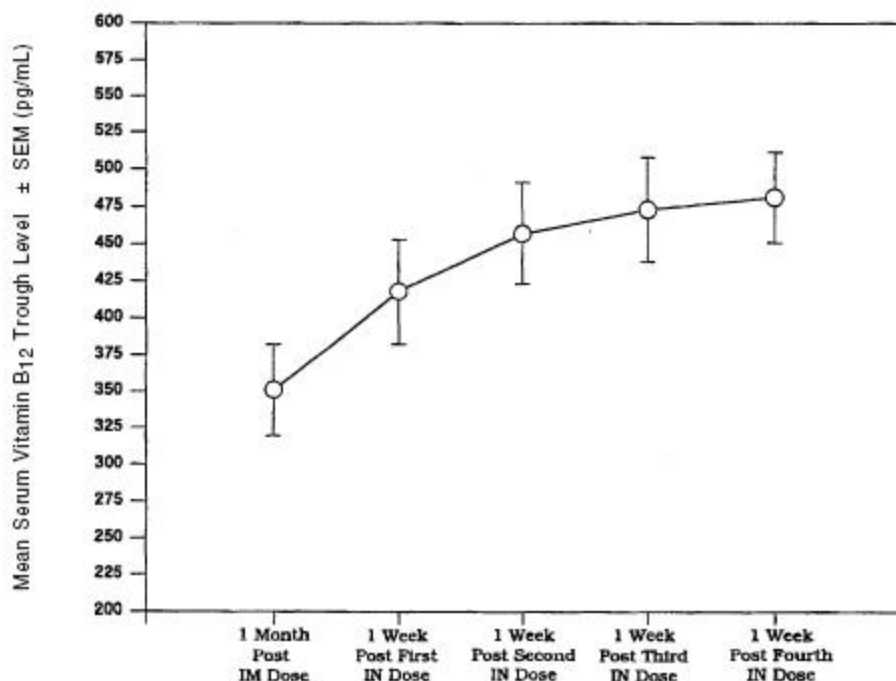


Figure. Vitamin B₁₂ Serum Trough Levels After Intramuscular Solution (IM) of 100 mcg and Nasal Gel (IN) Administration of 500 mcg Cyanocobalamin After Weekly Doses.

INDICATIONS AND USAGE

Nascobal Nasal Spray is indicated for the maintenance of normal hematologic status in pernicious anemia patients who are in remission following intramuscular vitamin B₁₂ therapy and who have no nervous system involvement.

Nascobal Nasal Spray is also indicated as a supplement for other vitamin B₁₂ deficiencies, including:

- I. Dietary deficiency of vitamin B₁₂ occurring in strict vegetarians (Isolated vitamin B₁₂ deficiency is very rare).
- II. Malabsorption of vitamin B₁₂ resulting from structural or functional damage to the stomach, where intrinsic factor is secreted, or to the ileum, where intrinsic factor facilitates vitamin B₁₂ absorption. These conditions include HIV infection, AIDS, Crohn's disease, tropical sprue, and nontropical sprue (idiopathic steatorrhea, gluten-induced enteropathy). Folate deficiency in these patients is usually more severe than vitamin B₁₂ deficiency.
- III. Inadequate secretion of intrinsic factor, resulting from lesions that destroy the gastric mucosa (ingestion of corrosives, extensive neoplasia), and a number of conditions associated with a variable degree of gastric atrophy (such as multiple sclerosis, HIV infection, AIDS, certain endocrine disorders, iron deficiency, and subtotal gastrectomy). Total gastrectomy always produces vitamin B₁₂ deficiency. Structural lesions leading to vitamin B₁₂ deficiency include regional ileitis, ileal resections, malignancies, etc.
- IV. Competition for vitamin B₁₂ by intestinal parasites or bacteria. The fish tapeworm (*Diphyllobothrium latum*) absorbs huge quantities of vitamin B₁₂ and infested patients often have associated gastric atrophy. The blind loop syndrome may produce deficiency of vitamin B₁₂ or folate.

V. Inadequate utilization of vitamin B₁₂. This may occur if antimetabolites for the vitamin are employed in the treatment of neoplasia.

It may be possible to treat the underlying disease by surgical correction of anatomic lesions leading to small bowel bacterial overgrowth, expulsion of fish tapeworm, discontinuation of drugs leading to vitamin malabsorption (see **Drug/Laboratory Test Interactions**), use of a gluten free diet in nontropical sprue, or administration of antibiotics in tropical sprue. Such measures remove the need for long-term administration of vitamin B₁₂.

Requirements of vitamin B₁₂ in excess of normal (due to pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, hepatic and renal disease) can usually be met with intranasal or oral supplementation.

Nascobal Nasal Spray is not suitable for vitamin B₁₂ absorption test (Schilling Test).

CONTRAINDICATION

Sensitivity to cobalt and/or vitamin B₁₂ or any component of the medication is a contraindication.

WARNINGS

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B₁₂ suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B₁₂. Folic acid is not a substitute for vitamin B₁₂ although it may improve vitamin B₁₂-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B₁₂-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

Anaphylactic shock and death have been reported after parenteral vitamin B₁₂ administration. No such reactions have been reported in clinical trials with Nascobal Nasal Spray or Nascobal Nasal Gel.

Blunted or impeded therapeutic response to vitamin B₁₂ may be due to such conditions as infection, uremia, drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

PRECAUTIONS

1. GENERAL

An intradermal test dose of parenteral vitamin B₁₂ is recommended before Nascobal Nasal Spray is administered to patients suspected of cyanocobalamin sensitivity. Vitamin B₁₂ deficiency that is allowed to progress for longer than three months may produce permanent degenerative lesions of the spinal cord. Doses of folic acid greater than 0.1 mg per day may result in hematologic remission in patients with vitamin B₁₂ deficiency. Neurologic manifestations will not be prevented with folic acid, and if not treated with vitamin B₁₂, irreversible damage will result.

Doses of vitamin B₁₂ exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

The validity of diagnostic vitamin B₁₂ or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

Vitamin B₁₂ is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B₁₂ could mask the true diagnosis.

Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B₁₂ therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.

Vitamin B₁₂ deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B₁₂ may unmask this condition.

If a patient is not properly maintained with Nascobal[®] Nasal Spray, intramuscular vitamin B₁₂ is necessary for adequate treatment of the patient. No single regimen fits all cases, and the status of the patient observed in follow-up is the final criterion for adequacy of therapy.

The effectiveness of Nascobal Nasal Spray in patients with nasal congestion, allergic rhinitis and upper respiratory infections has not been determined. Therefore, treatment with Nascobal Nasal Spray should be deferred until symptoms have subsided.

2. INFORMATION FOR PATIENTS

Patients with pernicious anemia should be instructed that they will require weekly intranasal administration of Nascobal Nasal Spray for the remainder of their lives. Failure to do so will result in return of the anemia and in development of incapacitating and irreversible damage to the nerves of the spinal cord. Also, patients should be warned about the danger of taking folic acid in place of vitamin B₁₂, because the former may prevent anemia but allow progression of subacute combined degeneration of the spinal cord. (Hot foods may cause nasal secretions and a resulting loss of medication; therefore, patients should be told to administer Nascobal Nasal Spray at least one hour before or one hour after ingestion of hot foods or liquids.)

A vegetarian diet which contains no animal products (including milk products or eggs) does not supply any vitamin B₁₂. Therefore, patients following such a diet should be advised to take Nascobal Nasal Spray weekly. The need for vitamin B₁₂ is increased by pregnancy and lactation. Deficiency has been recognized in infants of vegetarian mothers who were breast fed, even though the mothers had no symptoms of deficiency at the time.

Because the nasal dosage forms of vitamin B₁₂ have a lower absorption than intramuscular dosage, nasal dosage forms are administered weekly, rather than the monthly intramuscular dosage. As shown in the Figure above, at the end of a month, weekly nasal administration results in significantly higher serum vitamin B₁₂ levels than after intramuscular administration. The patient should also understand the importance of returning for follow-up blood tests every 3 to 6 months to confirm adequacy of the therapy. Careful instructions on the actuator assembly, removal of the safety clip, priming of the actuator and nasal administration of Nascobal Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient.

3. LABORATORY TESTS

Hematocrit, reticulocyte count, vitamin B₁₂, folate and iron levels should be obtained prior to treatment. If folate levels are low, folic acid should also be administered. All hematologic parameters should be normal when beginning treatment with Nascobal[®] Nasal Spray.

Vitamin B₁₂ blood levels and peripheral blood counts must be monitored initially at one month after the start of treatment with Nascobal[®] Nasal Spray, and then at intervals of 3 to 6 months.

A decline in the serum levels of B₁₂ after one month of treatment with B₁₂ nasal spray may indicate that the dose may need to be adjusted upward. Patients should be seen one month after each dose adjustment; continued low levels of serum B₁₂ may indicate that the patient is not a candidate for this mode of administration.

Patients with pernicious anemia have about 3 times the incidence of carcinoma of the stomach as in the general population, so appropriate tests for this condition should be carried out when indicated.

4. DRUG/LABORATORY TEST INTERACTIONS

Persons taking most antibiotics, methotrexate or pyrimethamine invalidate folic acid and vitamin B₁₂ diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B₁₂.

5. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term studies in animals to evaluate carcinogenic potential have not been done. There is no evidence from long-term use in patients with pernicious anemia that vitamin B₁₂ is carcinogenic. Pernicious anemia is associated with an increased incidence of carcinoma of the stomach, but this is believed to be related to the underlying pathology and not to treatment with vitamin B₁₂.

6. PREGNANCY

Pregnancy Category C: Animal reproduction studies have not been conducted with vitamin B₁₂. It is also not known whether vitamin B₁₂ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B₁₂ is an essential vitamin and requirements are increased during pregnancy. Amounts of vitamin B₁₂ that are recommended by the Food and Nutrition Board, National Academy of Science - National Research Council for pregnant women should be consumed during pregnancy.

7. NURSING MOTHERS

Vitamin B₁₂ appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B₁₂ blood level.

Amounts of vitamin B₁₂ that are recommended by the Food and Nutrition Board, National Academy of Science-National Research Council for lactating women should be consumed during lactation.

8. PEDIATRIC USE

Intake in pediatric patients should be in the amount recommended by the Food and Nutrition Board, National Academy of Science-National Research Council.

ADVERSE REACTIONS

The incidence of adverse experiences described in the Table below are based on data from a short-term clinical trial in vitamin B₁₂ deficient patients in hematologic remission receiving Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration (N=24) and intramuscular vitamin B₁₂ (N=25). In the pharmacokinetic study comparing Nascobal Nasal Spray and Nascobal Nasal Gel, the incidence of adverse events was similar.

Table. Adverse Experiences by Body System, Number of Patients and Number of Occurrences by Treatment Following Intramuscular and Intranasal Administration of Cyanocobalamin.

Body System	Adverse Experience	Number of Patients (Occurrences)	
		Vitamin B ₁₂ Nasal Gel, 500 mcgN=24	Intramuscular Vitamin B ₁₂ , 100 mcgN=25
Body as a Whole	Asthenia	1 (1)	4 (4)
	Back Pain	0 (0)	1 (1)
	Generalized Pain	0 (0)	2 (3)
	Headache	1 (2)*	5 (11)
	Infection [†]	3 (4)	3 (3)
Cardiovascular System	Peripheral Vascular Disorder	0 (0)	1 (1)
Digestive System	Dyspepsia	0 (0)	1 (2)
	Glossitis	1 (1)	0 (0)
	Nausea	1 (1)*	1 (1)
	Nausea & Vomiting	0 (0)	1 (1)
	Vomiting	0 (0)	1 (1)

Musculoskeletal System	Arthritis	0 (0)	2 (2)
	Myalgia	0 (0)	1 (1)
Nervous System	Abnormal Gait	0 (0)	1 (1)
	Anxiety	0 (0)	1 (1)*
	Dizziness	0 (0)	3 (3)
	Hypoesthesia	0 (0)	1 (1)
	Incoordination	0 (0)	1 (2)*
	Nervousness	0 (0)	1 (3)*
	Paresthesia	1 (1)	1 (1)
Respiratory System	Dyspnea	0 (0)	1 (1)
	Rhinitis	1 (1)*	2 (2)

*There may be a possible relationship between these adverse experiences and the study drugs. These adverse experiences could have also been produced by the patient's clinical state or other concomitant therapy.

†Sore throat, common cold

The intensity of the reported adverse experiences following the administration of Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B₁₂ were generally mild. One patient reported severe headache following intramuscular dosing. Similarly, a few adverse experiences of moderate intensity were reported following intramuscular dosing (two headaches and rhinitis; one dyspepsia, arthritis, and dizziness), and dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration (one headache, infection, and paresthesia).

The majority of the reported adverse experiences following dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration and intramuscular vitamin B₁₂ were judged to be intercurrent events. For the other reported adverse experiences, the relationship to study drug was judged as "possible" or "remote". Of the adverse experiences judged to be of "possible" relationship to the study drug, anxiety, incoordination, and nervousness were reported following intramuscular vitamin B₁₂ and headache, nausea, and rhinitis were reported following dosing with Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration.

The following adverse reactions have been reported with parenteral vitamin B₁₂:

Generalized: Anaphylactic shock and death (see **WARNINGS** and **PRECAUTIONS**).

Cardiovascular: Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

Hematological: Polycythemia vera.

Gastrointestinal: Mild transient diarrhea.

Dermatological: Itching; transitory exanthema.

Miscellaneous: Feeling of swelling of the entire body.

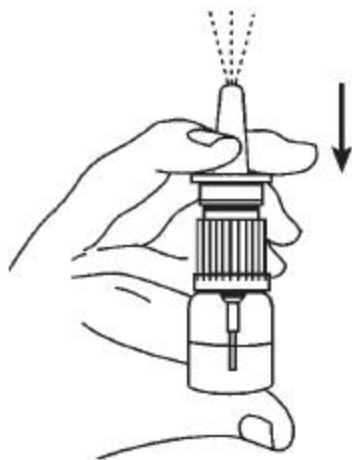
OVERDOSAGE

No overdosage has been reported with Nascobal Nasal Spray, Nascobal (Cyanocobalamin, USP) Gel for Intranasal Administration or parenteral vitamin B₁₂.

DOSAGE AND ADMINISTRATION

The recommended initial dose of Nascobal Nasal Spray is one spray (500 mcg) administered in ONE nostril once weekly. Nascobal Nasal Spray should be administered at least one hour before or one hour after ingestion of hot foods or liquids. Periodic monitoring of serum B₁₂ levels should be obtained to establish adequacy of therapy.

Before the first dose and administration, the pump must be primed. Remove the clear plastic cover and the plastic safety clip from the pump. To prime the pump, place nozzle between the first and second finger with the thumb on the bottom of the bottle. Pump the unit firmly and quickly until the first appearance of spray. Then prime the pump an additional 2 times. Now the nasal spray is ready for use. The unit must be re-primed before each dose. Prime the pump **once** immediately before each administration of doses 2 through 8.



See **LABORATORY TESTS** for monitoring B₁₂ levels and adjustment of dosage.

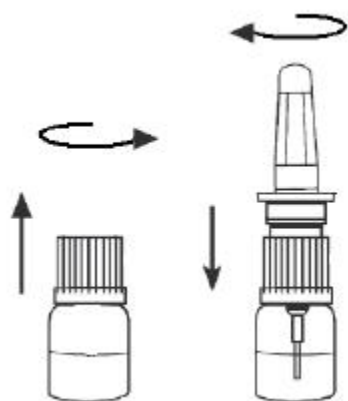
HOW SUPPLIED

Nascobal Nasal Spray is available as a spray in 3 mL glass bottles containing 2.3 mL of solution. It is available in a dosage strength of 500 mcg per actuation (0.1 mL/actuation). A screw-on actuator is provided. This actuator, following priming, will deliver 0.1 mL of the spray. Nascobal Nasal Spray is provided in a carton containing a nasal spray actuator with dust cover, a bottle of nasal spray solution, and a package insert. One bottle will deliver 8 doses (NDC 49884-270-14).

PHARMACIST ASSEMBLY INSTRUCTIONS FOR NASCOBAL NASAL SPRAY

The pharmacist should assemble the Nascobal Nasal Spray unit prior to dispensing to the patient, according to the following instructions:

1. Open the carton and remove the spray actuator and spray solution bottle.
2. Assemble Nascobal Nasal Spray by first unscrewing the white cap from the spray solution bottle and screwing the actuator unit tightly onto the bottle. Make sure the clear dust cover is on the pump unit.
3. Return the Nascobal Nasal Spray bottle to the carton for dispensing to the patient.



INFORMATION FOR PATIENTS

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STORAGE CONDITIONS

Protect from light. Keep covered in carton until ready to use. Store upright at controlled room temperature 15°C to 30°C (59°F to 86°F). Protect from freezing.

Distributed by:

Par Pharmaceutical, Inc
Spring Valley, NY 10977
OS270-01-01

Rev. 03/09

FOR NASAL USE ONLY

KEEP OUT OF REACH OF CHILDREN

Each 0.1 mL contains 500mcg Cyanocobalamin USP and the following inactive ingredients: Citric Acid USP, Sodium Citrate USP, Glycerin USP, Benzalkonium Chloride NF and Purified Water USP.

One bottle will deliver eight doses.

Read instructions carefully before using.

See package insert for complete prescribing information.

Store upright at controlled room temperature 15°-30° C (59°-86° F).

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL: NASCOBAL NASAL SPRAY 500MCG/SPRAY

NDC 49884-270-14

Nascobal® Nasal Spray

(Cyanocobalamin, USP)

500mcg/spray

2.3mL (8 sprays)

